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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/908,453	08/07/97	RUVKUN G	08472/704002

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EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	17

DATE MAILED: 05/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/908,453	Ruvkun et al
Examiner	**Group Art Unit**
Ram Shukla	1632

☒ Responsive to communication(s) filed on *Feb 22, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *8-13, 15-20, 29, and 30* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *8-13, 15-20, 29, and 30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed on 2-22-00 (Paper No. 16) is entered.

2. Amended claims 8, 9, 16, 18 and 20 have been entered. New claims 29 and 30 have been entered.

3. Claims 8-13, 15-20 and 29-30 are pending in the instant application.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Amended claims 8-11 and newly presented claims 29-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons set forth in the office action of 8-17-99 and further for reasons discussed below.

Applicant is referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, page 71427-71440 (also available at www.uspto.gov).

Amended claim 8 recites a purified DNA which encodes an AGE-1 polypeptide having PI3-kinase activity and said polypeptide has at least 50% amino acid sequence identity to the full length polypeptide of Seq ID NO 1 and comprises a p85 domain and a lipid kinase domain. Claim 9 is drawn to a purified DNA comprising an AGE-1 nucleic acid sequence which is at least 30% identical to the full length sequence of Seq ID NO 2 and wherein said DNA encodes an AGE-1 polypeptide having PI3-kinase activity, said polypeptide comprising a p85 domain and a lipid kinase domain. Claims 10 and 11 are drawn to vectors and cells comprising the purified

AGE-1 DNA of claims 8 or 9. Claim 13 recites the recombinant AGE-1 polypeptide produced by the method of claim 12. Claim 29 recites a purified DNA which encodes an AGE-1 polypeptide wherein said polypeptide comprising at least 50% of a list of amino acids at certain positions of Seq ID NO 1 and wherein said polypeptides comprise a p85 domain and a lipid kinase domain and said polypeptide has PI3-kinase activity. Claim 30 limits the DNA of claim 29 wherein said polypeptide comprises an identical amino acid in the equivalent position to Ala-827 of Seq ID NO 1.

As noted in the previous office action of 8-17-99, the specification only discloses the nucleotide sequence of Seq ID No 2 that encodes the polypeptide disclosed in Seq ID NO 1. The first condition of the written description requirement is not met because a representative number of species have not been described by their complete structure, Seq ID No 2 is the only species whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been the nucleotide sequence of all the polynucleotides that encode polypeptides that have at least 50% sequence identity with the sequence of Seq ID NO 1 or that have the different combination of amino acids at positions claimed in claim 29 or claim 30.

Response to Applicants arguments:

Applicants' arguments have been fully considered, however, they are not deemed persuasive. Applicants have argued that they have discovered what is a divergent PI3-kinase class and that the specification clearly describes what is claimed. However, these arguments are not persuasive because based on the disclosure in the specification at the date of the file of the application, Applicants did not have the possession of all the DNA sequences that encoded all the AGE-1 polypeptides, rather they only have the possession of the nucleic acid of Seq ID NO 2 that encodes the polypeptide of Seq ID NO 1. Just describing that a polypeptide has a certain domain does not establish that one has the nucleic acid sequence that encodes said polypeptide. The Applicants have argued that the specification on page 22 (lines 6-25) describes the domains of AGE-1, however, these arguments are not persuasive because said disclosure in the specification only compares the sequence of Seq ID No with those of the other known proteins in the database and how do sequences of Seq ID NO 1 compare with the sequence of known domains listed in the database. This in no way demonstrates that the Applicants had the

possession of all the polypeptides encompassed by the claimed invention that had certain domains. Applicants have questioned the basis of rejection based on the term "substantially pure" that the claim is not to an impurity, however, these arguments are not persuasive because while it is realized that the claim in not to an impurity, how can a DNA encode all the proteins present in an impure composition of a polypeptide.

In summary, the issue remains: with the information disclosed, does the specification reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and the answer is no, because the specification only discloses the nucleotide sequence of Seq ID NO 2 that encodes the polypeptide of Seq ID NO 1.

This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of cDNAs besides Seq ID No. 2 at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

6. Amended claims 8, 9, and originally presented claims 10-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons set forth in the previous office action of 8-17-99.

The invention of claims 8 -13 has been previously summarized in para 5 above. The method of claim 15 was summarized in the previous office action of 8-17-99. Claim 15 recites a method of identifying a compound that decreases the expression of an AGE-1 gene wherein a cell expressing AGE-1 DNA of claim 8 or 9 is contacted with a candidate compound and a decrease in AGE-1 gene expression identifies the modulatory compound.

As stated in the previous office action of 8-17-99, the specification is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have made all the claimed polynucleotide sequences, vectors, and host cells expressing all the claimed polynucleotide sequences and would have used those without undue experimentation.

Response to Applicants Arguments:

Applicants' arguments have been fully considered, however, they are not deemed persuasive.

Applicants have argued that the specification, on pages 26-27, provides guidance for cloning mammalian AGE-1 polypeptides and that cloning strategies, hybridization cloning and PCR cloning and exemplary AGE-1 sequences that are specific to cloning of AGE-1 nucleic acids have been disclosed. However, as noted in the previous office action, even if one had to assume that using various molecular biology techniques described in the specification in pages 26-27, an artisan would have been able to make these polynucleotides, would all the polypeptides encoded by the isolated polynucleotides have had any specific functions? In the absence of any function, how would an artisan have known how to use all these polynucleotides, expression vectors comprising these polynucleotide segments, host cells comprising these polynucleotide expression vectors, and producing the polypeptides encoded by these polynucleotides or preparing membranes of host cells expressing these polynucleotides? Furthermore, just because the claimed polypeptides have amino acid identity to a known protein, does not ensure that the polypeptide or its derived or cloned fragments would have the same function or even any function as that of the AGE-1 polypeptide. Neither the specification nor the prior art on record, at the time of the filing of the application, provides any guidance whether AGE-1 polypeptide has PI3-kinase activity. The only support for such activity is the observation that the polypeptide when compared with known proteins of the database has similarity to kinase domain. There is nothing on the record to show whether art recognized assay conditions would be sufficient to support kinase activity of AGE-1 polypeptide in vitro because no working examples of any such assay have been disclosed in the specification or in the prior art on record.

Therefore, the issues remains: only because a protein comprises a domain that has 37% sequence similarity with a given functional domain in another protein, will it have the activity of the said domain and as noted earlier, there is no evidence in the specification to demonstrate that the claimed peptides would have a kinase activity. Even if one may assume that the Seq ID NO 1 may have a kinase activity, how will a polypeptide that has 50% sequence identity (which may encompass a protein wherein 50% of the amino acids have been altered or have different sequence) may have the kinase activity or any of the claimed activities or domains. Therefore, it is not established whether the DNA or nucleic acids encompassed by the claimed invention will have a kinase activity, if so an artisan would not have known how to use such a nucleic acid or DNA, vector comprising said nucleic acid or DNA or cells comprising said vector because in the absence of function how would an artisan use these and for what.

Applicants have argued that there is no reasonable scientific basis to support the Patent Office's assertion that the present fails to enable one of skill in the art to obtain a reasonable number of DNAs recited in claims 8 and 9, however, these arguments are not deemed persuasive because the specification, the prior art on record, and Applicants arguments have not addressed the issues that the polynucleotides encompassed by the claimed invention would have PI3-kinase activity. Applicants have further argued that they have amended claims 8 and 9 to specify that AGE-1 DNAs falling under the present claims encoded polypeptides encoded polypeptides having PI3- kinase activity, and therefore, said DNA by necessity have PI3-kinase activity, however, if it is not established that the Seq ID NO 2 encoded protein has PI3-kinase activity, how would all the other polynucleotide encoded proteins have that activity.

Applicants have made similar arguments about vectors comprising sequence of claims 8 and 9 and cells comprising such vectors, however, as discussed above, if the function of the proteins was not known how would an artisan use such even if an artisan was able to make vectors or cells by following the teachings of the specification. Applicants also argued that methods for the generation of vectors, cells and recombinant proteins are routine in the field of molecular biology, however, these arguments are not persuasive because, in the absence of a function, how would an artisan know how to use said vectors, host cells, processes to make polypeptides or the polypeptides produced.

It is, therefore, concluded that the specification as filed is not enabling for the claimed invention as filed and an artisan would not have been able to practice the invention without undue experimentation.

7. Amended claims 16, 18, and 20 and originally presented claims 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons set forth in the previous office action of 8-17-99.

Amended claim 16 is directed to a method of identifying compounds that decrease AGE-1 PI3- kinase activity wherein a cell expressing an AGE-1 polypeptide is contacted with a candidate compound, and a decrease in the AGE-1 PI3-kinase activity is monitored for identifying the AGE-1 modulating compounds. The invention of claim 17 has been summarized in the previous office action. Claim 18 limits the invention of claim 15 or 16 wherein the AGE-1 polypeptide is from an animal. Claim 19 limits the invention of claim 15 or 16 wherein the method is carried out in a nematode or other animal. Claim 20 limits the invention of claim 15 or 16 wherein said method involves assaying AGE-1 PI3-kinase activity in vitro.

As disclosed in the previous office action, the specification as filed is not enabling for the claimed invention because the specification does not provide any evidence as to (i) what is the activity of the AGE-1 polypeptide; (ii) if the activity of AGE-1 polypeptide is not known, how would an artisan have assayed the AGE-1 activity in vitro; (iii) whether the polypeptides, that would have had 50% identity with the polypeptide disclosed in Seq ID No 1, would have the activity of AGE-1 polypeptide; (iv) whether the AGE-1 polypeptide from animals would have had the same activity as the AGE-1 polypeptide disclosed in Seq ID No 1; (v) whether an artisan would have been able to carry out the claimed method in any animal or nematodes? The specification does not provide any guidance as to how an artisan would have dealt with these problems and therefore, an artisan would not have been able to make and use the invention as claimed without undue experimentation.

Response to Applicant's Arguments:

Applicants arguments have been fully considered, however, they are not deemed persuasive because, these arguments do not persuasively respond to the points raised in the previous office action.

For example, the Applicants arguments do not address the issue: what is the activity of the AGE-1 polypeptide? Applicants have made a statement that "AGE-1 polypeptide is a PI3-kinase," however, there is nothing on the record to show that the said polypeptide has a kinase activity because the specification does not provide any evidence or working example, as to whether claimed AGE-1 polypeptide has kinase activity. Likewise Applicants arguments regarding other four issues listed above and in the previous office action are not persuasive because if it is not established that the AGE-1 polypeptide has a kinase activity, how can the issues regarding the activity of a protein produced in prokaryotic cells or purification of the polypeptide or in vitro assay conditions can be addressed because for all these assays one had to know what is the activity of the said polypeptide. Regarding Applicants' argument, that because bovine p110 has PI3-kinase activity, AGE-1 will also have PI3- kinase activity, it is noted that because the sequence of said p110 when compared with the sequence of AGE-2, shows only 13.4% overall identity and only 30.7% best local similarity. How can one correlate the activity of two proteins when they have only 13.4% sequence identity?

Likewise, regarding in vivo testing methods in animals, in the currently presented format, claimed invention would encompass all animals, however, neither the specification nor do Applicant's arguments not disclose what phenotype will be monitored in all animals, for example, what activity or phenotype of a mouse will be monitored if the method was to be performed in a mouse.

In conclusion, the specification as filed fails to provide sufficient guidance, working examples and evidence as to how an artisan of skill would have practiced the claimed invention without undue experimentation.

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 8-13,15-20, and 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 and their dependent claims are indefinite because it is unclear what can be considered "a purified DNA", for example, does it mean only one molecule of DNA or a certain preparation of purified DNA that may include some impurities. The use of the phrase "an isolated DNA segment" is suggested.

Claims 15, 16 and their dependent claims are indefinite because it is unclear what is meant by the phrase "a decrease in AGE-1 expression following contact with said candidate compound identifying a modulatory compound".

10. Claims 8-13, 15-20, and 29-30 are free of prior art because they are drawn to a nucleic acid of AGE-1 protein, a host cell expressing the claimed nucleotides and assay methods for identifying compounds that modulate AGE-1 polypeptides.

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Karen M. Hauda

Ram R. Shukla, Ph.D.

Karen M. Hauda
Patent Examiner